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(72) Inventors; and

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(74) Agents: **JANG, Soonhee et al.; ELI LILLY AND COMPANY, P. O. Box 6288, Indianapolis, Indiana 46206-6288 (US).**

(81) Designated States (unless otherwise indicated, for every kind of national protection available): **AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.**

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): **ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).**

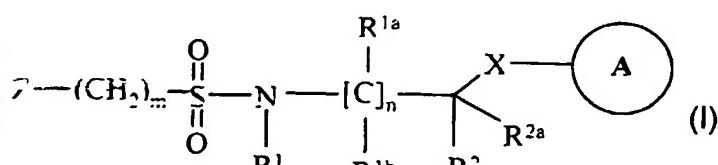
**Declarations under Rule 4.17:**

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ,*

*[Continued on next page]*

(54) Title: SULFONAMIDE DERIVATIVES AS PPAR MODULATORS



coagulopathy, hypertension, arteriosclerosis, and other disorders related to syndrome X and cardiovascular diseases.

(57) Abstract: The present invention is directed to a compound of Formula (I), and pharmaceutically acceptable salts, solvates, hydrates or stereoisomers thereof, which are useful in treating or preventing disorders mediated by a peroxisome proliferator activated receptor (PPAR) such as syndrome X, type II diabetes, hyperglycemia, hyperlipidemia, obesity, and cardiovascular diseases.

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EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID,  
IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,  
LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ,  
OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,  
TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA,  
ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ,  
SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ,  
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,  
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU,  
IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent  
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,  
SN, TD, TG)

— of inventorship (Rule 4.17(iv)) for US only

**Published:**

— with international search report

**(88) Date of publication of the international search report:**  
31 March 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>IPC 7 C07D333/62 C07D409/12 C07C311/29 C07C311/16 C07D213/71<br>C07D231/18 C07D213/74 C07D263/32 C07D333/34 C07D231/12<br>C07D277/36 C07D319/18 C07D311/13 C07D409/04 C07D307/79  |  |                           |  |  |  |          |  |                       |   |  |                           |   |   |                           |  |     |  |
|---|--|---------------------------|--|--|--|----------|--|-----------------------|---|--|---------------------------|---|---|---------------------------|--|-----|--|
| According to International Patent Classification (IPC) or to both national classification and IPC   |  |                           |  |  |  |          |  |                       |   |  |                           |   |   |                           |  |     |  |
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>IPC 7 C07D A61K A61P  |  |                           |  |  |  |          |  |                       |   |  |                           |   |   |                           |  |     |  |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched   |  |                           |  |  |  |          |  |                       |   |  |                           |   |   |                           |  |     |  |
| Electronic data base consulted during the international search (name of data base and, where practical, search terms used)<br>EPO-Internal, WPI Data, PAJ, BEILSTEIN Data   |  |                           |  |  |  |          |  |                       |   |  |                           |   |   |                           |  |     |  |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left; padding: 2px;">Category</th> <th style="text-align: left; padding: 2px;">Citation of document, with indication, where appropriate, of the relevant passages</th> <th style="text-align: left; padding: 2px;">Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td style="padding: 2px;">X</td> <td style="padding: 2px;">M. SATO ET. AL.: "Synthesis and evaluation of novel fluorinated sulotroban-related sulfonamide derivatives as thromboxane A<sub>2</sub> receptor antagonists." EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 30, 1995, pages 403-14, XP002296706 tables I-III</td> <td style="padding: 2px;">1-4,<br/>7-10,13,<br/>14,25</td> </tr> <tr> <td style="padding: 2px;">X</td> <td style="padding: 2px;">M. SATO ET. AL: "Asymmetric synthesis of the sulfoxide metabolite of ON-579 by the Kagan protocol." BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 7, no. 19, 1997, pages 2451-4, XP002296707 table I</td> <td style="padding: 2px;">1-4,<br/>7-10,13,<br/>14,25</td> </tr> <tr> <td></td> <td style="text-align: center; padding: 2px;">-/-</td> <td></td> </tr> </tbody> </table> |  |                           |  |  |  | Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. | X | M. SATO ET. AL.: "Synthesis and evaluation of novel fluorinated sulotroban-related sulfonamide derivatives as thromboxane A <sub>2</sub> receptor antagonists." EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 30, 1995, pages 403-14, XP002296706 tables I-III | 1-4,<br>7-10,13,<br>14,25 | X | M. SATO ET. AL: "Asymmetric synthesis of the sulfoxide metabolite of ON-579 by the Kagan protocol." BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 7, no. 19, 1997, pages 2451-4, XP002296707 table I | 1-4,<br>7-10,13,<br>14,25 |  | -/- |  |
| Category  | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.     |  |  |  |          |  |                       |   |  |                           |   |   |                           |  |     |  |
| X   | M. SATO ET. AL.: "Synthesis and evaluation of novel fluorinated sulotroban-related sulfonamide derivatives as thromboxane A <sub>2</sub> receptor antagonists." EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 30, 1995, pages 403-14, XP002296706 tables I-III | 1-4,<br>7-10,13,<br>14,25 |  |  |  |          |  |                       |   |  |                           |   |   |                           |  |     |  |
| X   | M. SATO ET. AL: "Asymmetric synthesis of the sulfoxide metabolite of ON-579 by the Kagan protocol." BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 7, no. 19, 1997, pages 2451-4, XP002296707 table I  | 1-4,<br>7-10,13,<br>14,25 |  |  |  |          |  |                       |   |  |                           |   |   |                           |  |     |  |
|   | -/-  |                           |  |  |  |          |  |                       |   |  |                           |   |   |                           |  |     |  |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.  |  |                           | <input checked="" type="checkbox"/> Patent family members are listed in annex. |  |  |          |  |                       |   |  |                           |   |   |                           |  |     |  |
| * Special categories of cited documents :<br>*A* document defining the general state of the art which is not considered to be of particular relevance<br>*E* earlier document but published on or after the International filing date<br>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)<br>*O* document referring to an oral disclosure, use, exhibition or other means<br>*P* document published prior to the International filing date but later than the priority date claimed  |  |                           |  |  |  |          |  |                       |   |  |                           |   |   |                           |  |     |  |
| Date of the actual completion of the International search   |  |                           | Date of mailing of the International search report                             |  |  |          |  |                       |   |  |                           |   |   |                           |  |     |  |
| 21 September 2004   |  |                           | 21/10/2004   |  |  |          |  |                       |   |  |                           |   |   |                           |  |     |  |
| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016  |  |                           | Authorized officer<br><br>Helps, I   |  |  |          |  |                       |   |  |                           |   |   |                           |  |     |  |

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |  |                              |
|--|--|------------------------------|
| Category   | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.        |
| X  | K. SHINOZAKI ET. AL.: "Synthesis and thromboxane A2 antagonistic activity of indane derivatives." BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 9, 1999, pages 401-6, XP002296708 tables 1,2  | 1,25                         |
| X  | M. SATO ET. AL: "Synthesis and evaluation of novel sulfonamide derivatives as thromboxane A2 receptor antagonists I." EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 29, 1994, pages 185-90, XP002296709 tables I,II  | 1-4,<br>7-10,13,<br>14,17,25 |
| X  | J. P. BERLOT ET. AL.: "Preparation of a dansylated fibrate, a new fluorescent tool to study peroxisome proliferation. Effect on hepatic-derived lines." BIOCHEMIE, vol. 79, 1997, pages 145-50, XP002296710 page 148   | 1-4,<br>7-10,13              |
| X  | K. G. LIU ET. AL.: "Identification of a Series of PPARgamma/delta dual Agonists Via Solid-Phase Parallel Synthesis." BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 11, 2001, pages 2959-62, XP002296711 page 2960, column 1, paragraph 1 - page 2961, column 1, paragraph 1 | 1-4,<br>7-10,13,<br>14       |
| X  | US 6 518 290 B1 (SIERRA)<br>11 February 2003 (2003-02-11)  | 1                            |
| A  | intermediate compound D, claims;<br>examples   | 1-40                         |
| X  | US 6 306 854 B1 (BROWN ET. AL.)<br>23 October 2001 (2001-10-23)  | 1                            |
| A  | intermediate compound 14, claims;<br>examples  | 1-40                         |
| A  | US 6 369 098 B1 (PERSHADSINGH ET. AL.)<br>9 April 2002 (2002-04-09)<br>column 1 - column 3; claims; examples   | 1-40                         |
| P,A  | WO 03/072099 A (ELI LILLY)<br>4 September 2003 (2003-09-04)<br>page 1, line 1 - page 2, line 7; claims;<br>examples  | 1-40                         |
| A  | EP 1 167 357 A (SANKYO)<br>2 January 2002 (2002-01-02)<br>page 1, line 1 - page 2, line 20; claims;<br>examples  | 1-40                         |
|  |  | -/-                          |

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages                     | Relevant to claim No. |
|----------|--|-----------------------|
| A        | US 6 248 781 B1 (JEPPESEN ET. AL.)<br>19 June 2001 (2001-06-19)<br>column 1; claims; examples<br>----- | 1-40                  |

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2004/002015

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 27-39 (part)  
because they relate to subject matter not required to be searched by this Authority, namely:  

Although claims 27-39 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

## Information on patent family members

International Application No

T/US2004/002015

| Patent document cited in search report |    | Publication date |  | Patent family member(s)   |  | Publication date   |
|--|----|------------------|--|---|--|--|
| US 6518290                             | B1 | 11-02-2003       | AT<br>AU<br>AU<br>BR<br>CA<br>DE<br>DK<br>EP<br>HU<br>JP<br>NO<br>PL<br>CN<br>CZ<br>WO<br>TR<br>TW<br>ZA | 265442 T<br>758758 B2<br>2003001 A<br>0016067 A<br>2393190 A1<br>60010333 D1<br>1244642 T3<br>1244642 A1<br>0203532 A2<br>2003515597 T<br>20022467 A<br>356772 A1<br>1402716 T<br>20021903 A3<br>0140207 A1<br>200201473 T2<br>555753 B<br>200204241 A        |  | 15-05-2004<br>27-03-2003<br>12-06-2001<br>06-08-2002<br>07-06-2001<br>03-06-2004<br>16-08-2004<br>02-10-2002<br>28-02-2003<br>07-05-2003<br>26-07-2002<br>12-07-2004<br>12-03-2003<br>15-01-2003<br>07-06-2001<br>23-09-2002<br>01-10-2003<br>02-07-2003 |
| US 6306854                             | B1 | 23-10-2001       | AU<br>EP<br>WO<br>JP   | 6350699 A<br>1149063 A2<br>0023407 A2<br>2002527496 T   |  | 08-05-2000<br>31-10-2001<br>27-04-2000<br>27-08-2002   |
| US 6369098                             | B1 | 09-04-2002       | AU<br>WO<br>US<br>AU<br>WO   | 7995300 A<br>0125226 A1<br>2002019344 A1<br>8827101 A<br>0213812 A1   |  | 10-05-2001<br>12-04-2001<br>14-02-2002<br>25-02-2002<br>21-02-2002   |
| WO 03072099                            | A  | 04-09-2003       | WO   | 03072099 A1   |  | 04-09-2003   |
| EP 1167357                             | A  | 02-01-2002       | AU<br>AU<br>BR<br>CA<br>EP<br>NO<br>NZ<br>PL<br>US<br>US<br>CN<br>CZ<br>HU<br>WO<br>JP<br>RU<br>TR<br>ZA | 760163 B2<br>3670700 A<br>0009593 A<br>2369871 A1<br>1167357 A1<br>20014849 A<br>514661 A<br>351898 A1<br>2004002512 A1<br>2003069294 A1<br>1353694 T<br>20013593 A3<br>0200895 A2<br>0059889 A1<br>2001097955 A<br>2219172 C2<br>200102908 T2<br>200108168 A |  | 08-05-2003<br>23-10-2000<br>18-06-2002<br>12-10-2000<br>02-01-2002<br>27-11-2001<br>30-06-2003<br>30-06-2003<br>01-01-2004<br>10-04-2003<br>12-06-2002<br>13-03-2002<br>28-11-2002<br>12-10-2000<br>10-04-2001<br>20-12-2003<br>22-04-2002<br>18-02-2003 |
| US 6248781                             | B1 | 19-06-2001       | US<br>US<br>US<br>AU<br>WO<br>EP<br>JP   | 2001031762 A1<br>2001031764 A1<br>2001031786 A1<br>6325899 A<br>0023417 A1<br>1123269 A1<br>2002527503 T  |  | 18-10-2001<br>18-10-2001<br>18-10-2001<br>08-05-2000<br>27-04-2000<br>16-08-2001<br>27-08-2002   |